Arterial fragility in kyphoscoliotic Ehlers-Danlos syndrome

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Abstract: Pathogenic variants in the lysyl-hydroxylase-1 gene (PLOD1) are responsible for the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS). The disease is classically responsible for severe hypotonia at birth, progressive kyphoscoliosis, generalised joint hypermobility and scleral fragility. Arterial fragility is an important feature of the disease, but its characterisation remains limited. We report the clinical history of a 41-year-old woman who presented repeated arterial accidents, which occurred in previously normal medium size arteries within a limited time span of 2 years. Molecular investigations revealed compound heterozygosity for two PLOD1 gene deletions of exons 11-12 and 14-15. Arterial fragility is an important characteristic of kyphoscoliotic EDS. It manifests as spontaneous arterial rupture, dissections and dissecting aneurysms which may occur even during early childhood. This fragility is particularly likely to manifest during surgical intervention. Early medical management and surveillance may be indicated, but its modalities remain to be defined.

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TITLE OF CASE ***Do not include "a case report"***

Arterial fragility in kyphoscoliotic Ehlers-Danlos syndrome

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

Pathogenic variants in the lysyl-hydroxylase-1 gene (PLOD1) are responsible for the kyphoscoliotic type of Ehlers-Danlos syndrome (EDS). The disease is classically responsible for severe hypotonia at birth, progressive kyphoscoliosis, generalized joint hypermobility and scleral fragility. Arterial fragility is an important feature of the disease, but its characterization remains limited. We report the clinical history of a 47 year-old woman who presented repeated arterial accidents, which occurred in previously normal medium size arteries within a limited time span of 2 years. Molecular investigations revealed compound heterozygosity for two PLOD1 gene deletions of exons 11-12 and 14-15. Arterial fragility is an important characteristic of kyphoscoliotic EDS. It manifests as spontaneous arterial rupture, dissections and dissecting aneurysms which may occur even during early childhood. This fragility is particularly likely to manifest during surgical intervention. Early medical management and surveillance may be indicated, but its modalities remain to be defined.

BACKGROUND ***Why you think this case is important – why did you write it up?***

The kyphoscoliotic form of the Ehlers-Danlos syndrome (EDS; EDS type VI; former EDS type VIA; OMIM#225400) is a rare autosomic recessive connective tissue disorder due to mutations of the lysyl-hydroxylase-1 gene (*PLOD1*)[1]. The characteristic features of the disease are severe hypotonia at birth, progressive kyphoscoliosis, generalized joint hypermobility and scleral fragility that may lead to rupture of the ocular globe[2]. The presence of three of these clinical criteria is suggestive of the disease and indicates laboratory testing[3]. Further diagnostic criteria are tissue/skin fragility that may lead to atrophic scars and bruising, a marfanoid habitus, arterial

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rupture, microcornea, osteopenia and affected sibs[4]. The prevalence of kyphoscoliotic EDS remains unknown. Estimates of incidence are 1:100 000 live-births with a carrier frequency estimated to be 1:150. Pathogenic variants of the PLOD1 gene are characterized by a deficient activity of collagen lysyl-hydroxylase-1 (or procollagen-lysine 2-oxoglutarate 5-dioxygenase 1) leading to a defect in hydroxylation of collagen lysyl residues and ultimately to an impaired collagen crosslink formation. The diagnosis of kyphoscoliotic EDS can be made by measuring the ratio of urinary lysyl-pyridinoline to hydroxylysyl-pyridinoline (LP/HP) which is expected to be increased in case of a deficient lysyl-hydroxylase-1. Activity of the enzyme can also be tested in cultured skin fibroblasts[5]. Formal diagnosis is also obtained by genetic testing of the *PLOD1* alleles. Kyphoscoliotic EDS has been associated with arterial fragility, but - unlike vascular EDS - arterial ruptures seem to be more prevalent than dissections, and children seem particularly at risk. We report the arterial involvement observed in a 47 year-old woman with kyphoscoliotic EDS. The literature in respect of vascular fragility is reviewed.

CASE PRESENTATION ***Presenting features, medical/social/family history***

A 41 year-old woman was referred to our department for suspicion of connective tissue disorder, following the occurrence of a spontaneous right tibial anterior artery dissection. The dissection was discovered in a context of acute calf pain without identified trauma. Complementary work-up of the arterial tree evidenced a dissecting aneurysm of the celiac trunk, with a flap extending to the superior mesenteric artery (SMA) (as a consequence of an anatomic variation, the SMA originated from the celiac trunk). Two-year prior arterial monitoring had not revealed any arterial defect. Her medical history was relevant for generalized muscle hypotonia at birth, bilateral congenital dislocation of the hip, delayed gross motor development (independent walking at the age of 9 years) and rapidly evolving kyphoscoliosis. Three ocular ruptures occurred at ages 21, 25 and 27 years, respectively. All ruptures occurred following minor trauma. The right eye ruptured twice, the left eye once only. Sympathic ophtalmia complicated the left ocular rupture and resulted in complete loss of vision of the left eye despite adequate treatment. Her family

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history was remarkable by the death at the age of 9-years of her only and younger sister, by spontaneous abdominal aortic rupture. Her phenotype was similar to her older sister's.

INVESTIGATIONS ***If relevant***

Physical examination evidenced major cutaneous fragility (easy bruising) and dystrophic scars. Skin elasticity was significantly increased associated with a soft, velvety consistency. She furthermore presented a severe kyphoscoliosis and diffuse joint hypermobility (Beighton score 8/9) with instability, particularly of the left shoulder (recurrent dislocations). Further osteoarticular signs were pes planus and minor pectus excavatum (Figure 1). Echocardiography revealed a minor dysplasia of the mitral valve (anterior leaflet), without significant prolapse. Notably, high resolution echo-tracking recorded an important reduction of the carotid intima-media thickness (453µm), and a consequent increase of steady circumferential wall stress (75kPa). Haloplex target enrichment and next generation sequencing of *PLOD1* revealed compound heterozygous deletions of exons 11-12 and exons 14-15 (c.[(1097+1_1098-1)_(1328+1_1329-1)del];[(1470+1_1471-1)_(1650+1_1651-1)del]). These deletions were novel and submitted in the dedicated Leiden Open Variation Database (LOVD, http://www.LOVD.nl/PLOD1) Urinalysis showed a characteristic increase of the Deoxypyridinoline/Pyridinoline ratio to 10.4 (normal value LP/HP: 0.2 ± 0.03 in healthy individuals at any age), confirming the diagnosis of kyphoscoliotic EDS.

DIFFERENTIAL DIAGNOSIS ***If relevant***

TREATMENT ***If relevant***

OUTCOME AND FOLLOW-UP

The anterior tibial artery aneurysm was managed medically and resulted in minimal sequellae at the site of dissection. The dissecting aneurysm of the celiac trunk also remained stable and a complete regression of the extension of the dissection to the SMA was noted. Two years later, the patient presented with similar pain in the left calf. Doppler ultrasound documented a left tibial anterior dissecting aneurysm. This second clinical event also resolved medically. Celiprolol was

initiated and up-titrated to the optimally tolerated dose in prevention of further arterial events. The patient remained clinically silent to this day (4 years follow-up) and systematic arterial monitoring did not evidence further silent arterial defects.

DISCUSSION ***Include a very brief review of similar published cases***

Kyphoscoliotic EDS is a rare inherited connective tissue disorder, that appears less prevalent than vascular EDS, but with whom it has in common exceptional vascular fragility[6]. Indeed, patients are at risk of spontaneous arterial rupture that may occur at any age, particularly during childhood. This early expression of arterial fragility seems more common than in patients with vascular EDS, which are typically free of symptoms during early childhood[7]. Our case corroborates these findings and illustrates well the potential severity of kyphoscoliotic EDS. Indeed, the proband's family tree suggests that her sister had the same condition and died at the age of 9 years by spontaneous abdominal aortic rupture. By contrast, the proband developed an acute arterial event at the age of 41 years only. The existence of such phenotypic variability within one family has been reported previously for other features, but not in relation with arterial accidents. Rohrbach et al. submitted that kyphoscoliosis might not correlate with genotype and underlined the interfamilial and intrafamilial variability[8]. In regards of this extreme variability, vascular monitoring may be indicated at diagnosis, throughout the patient's life, both in probands and in affected sibs. Its precise modalities however remain to be defined.

The patient reported here is to our best knowledge the oldest reported kyphoscoliotic EDS patient, and the first with recurrent spontaneous dissections in medium size arteries without rupture. Due to the rarity of the disease and in the absence of large characterized patient cohorts, the incidence of arterial accidents in kyphoscoliotic EDS is unknown. However, the predominance of reports of traumatic arterial accidents highlight the potential vascular fragility of these patients, and make the occurrence of spontaneous, recurrent arterial accidents (dissection, dissecting aneurysm or rupture) all the more likely, as acknowledged by current diagnostic criteria[9]. In 1989, Wenstrup et al. reviewed the clinical characteristics of 10 patients with lysyl-hydroxylase deficiency. Ruptures of the femoral, intra-thoracic and vertebral arteries were

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reported[10]. Since the molecular characterization of kyphoscoliotic EDS in 2000, only two cases with molecularly proven pathogenic variants and arterial involvement have been reported[11]. We also note a fatal case of the superior vena cava rupture after extubation in an 8 year-old girl with molecularly proven disease, underlining again the particular vascular phenotype of the disease (i.e. including venous and arterial lesions)[12]. Published cases of vascular events in kyphoscoliotic EDS patients with sufficient characterization are reported in Table 1. Medicine-related illness and the risk of invasive procedures characterize the majority of reported cases. Spine surgery, likely because of its complexity and the length of the procedures, has a particularly high morbidity. However, in diagnosed patients, using a multidisciplinary approach in the management of the peri-operative period, the patient outcome may be significantly improved[12].

Table 1. Review of type VI Ehlers-Danlos syndromes with vascular events.

Patient	Sex	Age	Diagnosis				Type of accident	Lesion
		(years)	*compatible phenotype*	*urinary LP/HP elevation*	*cultured skin fibroblasts*	*molecular analysis*		
P1 [13]	M	10	+	ukn	+	ukn	V	Internal jugular vein ectasia post-catheterism
P2 [8]	M	27	+	+	ukn	+	A	Spontaneous dissection of coronary arteries during coronary angiography
P3 [14]	F	ukn	+	+	ukn	ukn	A	Right iliac artery rupture at delivery
P4 [12]	F	8	+	ukn	ukn	+	V	Rupture of the superior vena cava after extubation
P5 [15]	M	20	+	ukn	ukn	ukn	A	Coeliac trunk occlusion after spinal surgery (mechanism undisclosed)
P6 [16]	M	32	+	ukn	ukn	ukn	A / V	Profundal femoral artery rupture, femoral false aneurysm (access site), femoral venous rupture, splanchnic artery rupture (30 years), stroke (12 years) (mechanism undisclosed)

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P7 [17]	M	24	+	ukn	ukn	ukn	A	Traumatic aortic dissection, popliteal artery aneurysm (age undisclosed)
P8 [11]	M	12	+	+	ukn	+	A	Brachial artery rupture, profundal femoral artery rupture (11 years) and iliac artery rupture (9 years)
P9 [10]	ukn	ukn	+	ukn	+	ukn	A	Vertebral artery rupture
P10 [10]	ukn	ukn	+	ukn	+	ukn	A	Multiple ruptures of the femoral artery and repeated spontaneous intrathoracic arterial ruptures
P11 [18]	F	13	+	ukn	+	ukn	A / V	Abdominal aorta and iliac artery rupture, common iliac vein rupture during spine surgery
P12 [18]	F	13	+	ukn	+	ukn	A	Intraoperative superior gluteal artery rupture (spine surgery)

ukn : unknown, A : arterial; V : venous

Since patients with kyphoscoliotic EDS are exposed to acute, possibly life-threatening arterial accidents, it is of critical importance to determine whether it is possible to identify patients that are particularly at risk, and that may benefit from specific monitoring and medical intervention. The high resolution echotracking findings made in our patient suggest the existence of a detectable predisposition for arterial events. Indeed, Boutouyrie et al. showed that patients with vascular EDS have a distinctive arterial phenotype, characterized by decreased intima-media thickness of elastic arteries, which in turn results in an increase of arterial wall stress[19]. Similar findings were made in our patient, suggesting that arteries of kyphoscoliotic EDS patients with arterial fragility may have similar biomechanical characteristics of elastic arteries than vascular EDS patients. Further investigations on larger patient numbers are necessary to further characterize this specific arterial phenotype.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- Patients with kyphoscoliotic EDS are not only exposed to life-threatening arterial ruptures, but also to spontaneous dissections of medium size arteries.

- Further investigations are needed to identify determinants of intrafamilial variability in regards of arterial fragility.
- Qualititative assessment by high resolution echotracking of elastic artery properties may help identify patients/families that are particularly at risk and these patients may benefit from medical intervention to prevent arterial accidents.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Figure 1. Dysmorphic features of the present case.

The patient shows kyphoscoliosis with dolichostenomelia, pes planus, dystrophic scars and ecchymosis (a and b). She also present skin hyperlaxity (c).

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

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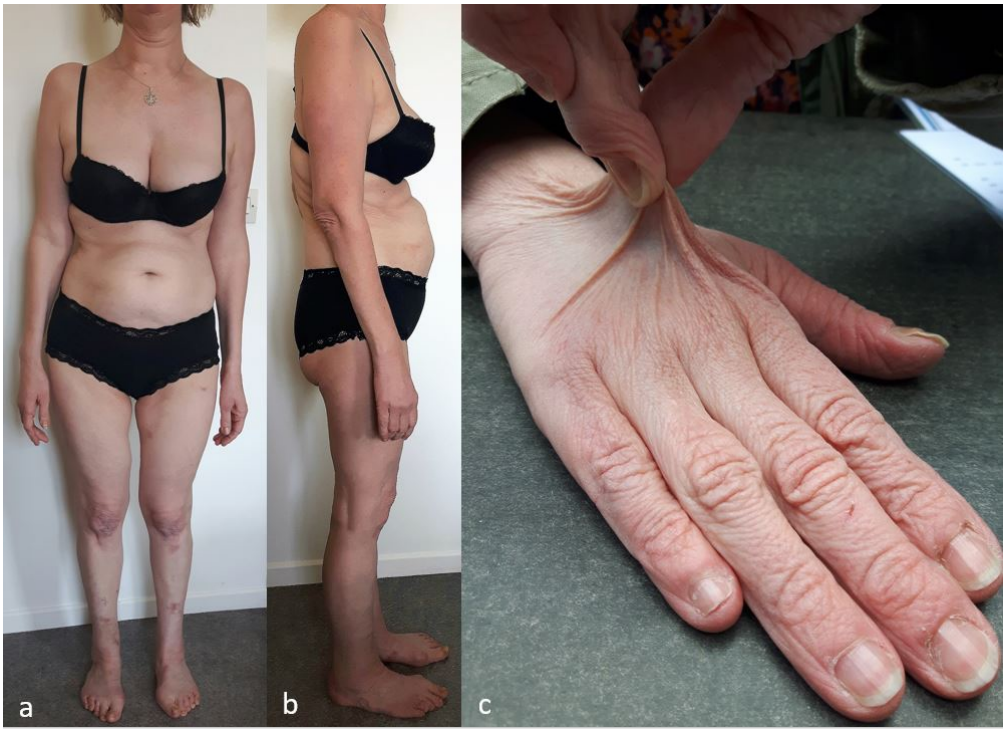

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